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(54) Title: NOVEL ORAL GENERAL ANESTHETICS AND METABOLITICALLY RESISTANT ANTICONVULSANTS

(57) Abstract: The present invention is directed to novel themisone derivative compounds that have been modified to prevent the formation of the toxic metabolite, 2-phenyl-acrylamide. Compositions comprising such derivative compounds have activity as anesthetics and as neuroprotective agents.

Novel Oral General Anesthetics and Metabolitically Resistant Anticonvulsants

Related Applications

This application claims priority under 35 USC §119(e) to US Provisional Application Serial Nos. 60/284,040, filed April 16, 2001, 60/333,603, filed November 27, 2001 and 60/354,181, filed February 4, 2002, the disclosures of which are incorporated herein.

Field of the Invention

The present invention is directed to novel derivatives of α-hydroxy-α-methylbenzeneacetamide (themisone), and the use of such derivatives as therapeutic agents. More particularly, compositions comprising the present themisone derivatives can be administered for reducing the incidence and severity of seizures and for use as a general anesthetic.

Background of the Invention

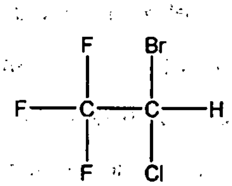
Many compositions are available for sedating patients or, in larger dosages, for inducing surgical anethesia in patients. These materials are used alone or in combination with other agents, such as nitrous oxide, to induce narcosis and to raise the patients pain threshold so that the patient can withstand surgical procedures. Likewise in smaller doses, these materials can reduce anxiety and generally sedate the patient. For example the following compounds are in general use as sedative and anesthetic agents: thiopental sodium, 5-allyl-1-methyl-5-(1-methyl-2-pentynyl) barbituric acid sodium salt (brevitol), 2-bromo-2-chloro-1,1,1-trifloroethane (halothane), and the like.

Most anesthetic and sedative agents, in addition to their beneficial effects, also lower certain body functions, such as respiration, blood pressure and heart action. Lowered body functions may sometimes lead to complications, particularly in older patients and in patients suffering from cardiac and vascular diseases and diseases of the kidneys and liver. Likewise, reduction in blood pressure may also lead to circulatory insufficiency during the surgical procedures which, unless alleviated, may do serious harm even to patients who have previously exhibited no

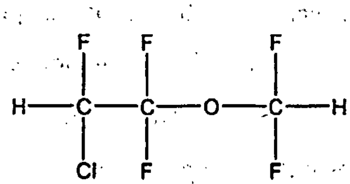
signs of heart, kidney or liver disfunction.

General anesthesia, administered as an inhaled or intravenous agent, for a surgical operation involves analgesia, amnesia, loss of consciousness, motionlessness and abolition of autonomic responses. The mechanism of action is still not completely understood, but most general anesthetics act at multiple molecular sites. The potential mechanisms of anesthesia action include protein receptor, lipid and ion channels. As the solubility of anesthetics increases in oil, so does the potency leading to the lipid theory developed by Meyer and Overton. There is also a correlation between anesthesia potency and the ability of the anesthetic to inhibit the enzyme activity of the protein, for example in firefly luciferase, a model used for studying anesthesia. In addition, potentiation of the inhibitory response, mediated by the neurotransmitter GABA (gamma-aminobutyric acid), dampens neuronal excitability placing the GABA receptor as a potential receptor site for anesthetic action. GABA is the major mediator of inhibitory synaptic transmission, and a family of ligand-gated chloride channel proteins. Other theories include NMDA and ligand-gated ion channels as a receptor. There is sufficient evidence supporting the blockade of Na^+ channels and the activation of K^+ channels.

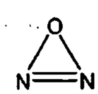
The effects of anesthesia depend on the concentration at the site of action, although concentrations cannot be measured in the brain of humans, therefore the concentration in the blood or expired gas (for inhaled anesthetics) is evaluated. Current inhaled general anesthetics (including, halothane enflurane, nitrous oxide, desflurane, isoflurane and sevoflurane, shown below) have a low therapeutic index (usually 2-3), hence the discovery of a new structural class would help in the development of safer anesthetics.



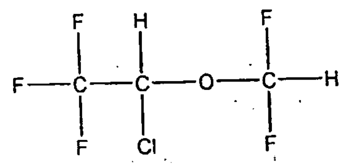
Halothane



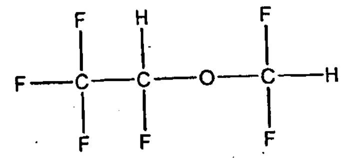
Enflurane



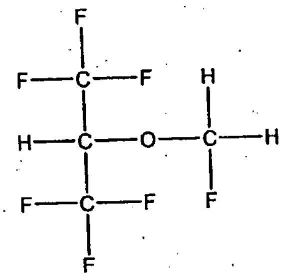
Nitrous Oxide



Isoflurane

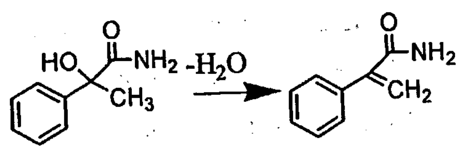


Desflurane



Sevoflurane

The present invention is directed to derivatives of themisone, that have been found to have anticonvulsant and anesthetic activity. Themisone, also known as Atrolactamide, was found in the 1950's to be a very potent anticonvulsant. The racemic mixture protected 4 out of 4 mice against seizures at 250 mg/kg, however the compound was toxic (blood dyscrasias, rash). Applicants believe the toxicity of this compound results from the formation of 2-phenyl-acrylamide by an elimination reaction as shown below:



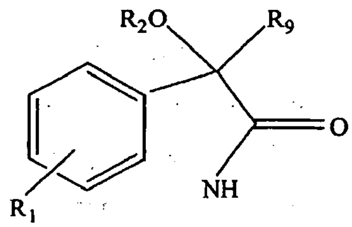
Themisone

2-phenyl-acrylamide
Potential toxic metabolite

To prevent the formation of this potential metabolite *in vivo*, applicants have designed and synthesized derivatives of themisone that prevent the elimination and potential formation of 2-phenyl-acrylamide, a potential toxic metabolite. These compounds have been found to exhibit both anti-convulsant activity as well as anesthetic acitivity. Accordingly, one aspect of the present invention is directed to novel themisone derivatives that are blocked from forming 2-phenyl-acrylamide and the use of such compounds for reducing the incidence and severity of seizures and for use as a general anesthetic.

Summary of the Invention

The present invention is directed to compounds having a general structure selected from the group consisting of:



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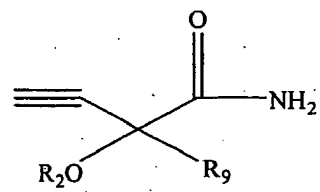

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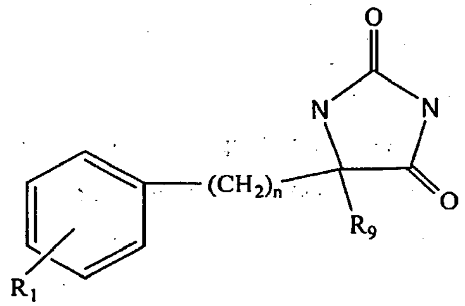


wherein R_1 is selected from the group consisting of H, halo, alkyl, haloalkyl, NH_2 and C_1-C_4 alkoxy; R_2 is H or alkyl; R_9 is optionally substituted aryl or haloalkyl; and n is an integer ranging from 1-3, and the use of such compounds as a sedative/anaesthetic or an anticonvulsive agent.

Brief Description of the Drawings

Fig. 1 is a graph plotting the partition coefficient, P (in log P) vs minimum alveolar concentration (MAC) and representing the anesthetic effects of the themisone derivatives (indicated by a reduction in the threshold of Isoflurane anesthesia).

Fig. 2 is a table listing the data produced during anticonvulsant testing of orally administered themisone and compound **17** in mice. The model examines the compound's ability to stop the spread of seizures induced by a maximal electroshock (MES) test, where corneal electrode implants are primed with a drop of electrolyte solution and an electrical stimulus is delivered for 0.2 second.

Fig. 3 is a table listing the data produced during anticonvulsant testing (using a subcutaneous metrazol test) of intraperitoneal, (i.p.) administered themisone and compound **17** in mice. The subcutaneous metrazol test (scMet) is conducted using a convulsant dose of pentylenetetrazol at the peak effect time of the compound.

Fig. 4 is a table listing the data produced from a toxicity test (TOX). The animals walk on a spinning rod for varying lengths of time to check for the loss of righting reflex or other toxic effects.

Fig. 5 is a table listing the MES ED_{50}, ScMet ED_{50} and Rotorod TD_{50} values for mice orally administered either compound **17** or phenytoid.

Fig. 6 is a graph plotting the heart rate vs dose and representing the effects of the presence or absence of ICM-I-40N (**17**) on heart rate during Isoflurane anesthesia.

Fig. 7 is a graph plotting the mean blood pressure vs dose and representing the effects of the presence or absence of ICM-I-40N (**17**) on blood pressure during Isoflurane anesthesia.

Fig. 8 is a graph plotting the percent MAC reduction vs dose and representing the reduction in the threshold of Isoflurane anesthesia following the administration of ICM-I-40N (●), ICM-1-76D (O), ICM-1-22 (■) and ICM-1-135 (□).

Detailed Description of the Invention

Definitions

In describing and claiming the invention, the following terminology will be used in accordance with the definitions set forth below.

As used herein, the term "purified" and like terms relate to the isolation of a molecule or compound in a form that is substantially free of contaminants normally associated with the molecule or compound in a native or natural environment.

As used herein, the term "treating" includes prophylaxis of the specific disorder or condition, or alleviation of the symptoms associated with a specific disorder or condition and/or preventing or eliminating said symptoms.

As used herein, the term "halogen" means Cl, Br, F, and I. Especially preferred halogens include Cl, Br, and F. The term "haloalkyl" as used herein refers to a C_1 -C_n alkyl radical bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

The term "C_1 -C_n alkyl" wherein n is an integer, as used herein, represents a branched or linear alkyl group having from one to the specified number of carbon atoms. Typically C_1 -C_6 alkyl groups include, but are not limited to, methyl,

ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and the like.

The term "C_2 -C_n alkenyl" wherein n is an integer, as used herein, represents an olefinically unsaturated branched or linear group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, 1-propenyl, 2-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, and the like.

The term "C_2 -C_n alkynyl" wherein n is an integer refers to an unsaturated branched or linear group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, and the like.

The term "C_3-C_n cycloalkyl" wherein n is an integer refers to cyclic non-aryl group, for example C_3-C_8 cycloalkyl, represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term "lower alkyl" as used herein refers to branched or straight chain alkyl groups comprising one to eight carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, neopentyl and the like.

As used herein, the term "optionally substituted" refers to from zero to four substituents, wherein the substituents are each independently selected. Each of the independently selected substituents may be the same or different than other substituents.

As used herein the term "aryl" refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, benzyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like. "Optionally substituted aryl" includes aryl compounds having from zero to four substituents, and "substituted aryl" includes aryl compounds having one to three substituents. The term (C_5-C_8 alkyl)aryl refers to any aryl group which is attached to the parent moiety via the alkyl group.

The term "heterocyclic group" refers to a mono- or bicyclic carbocyclic ring system containing from one to three heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, and nitrogen.

As used herein the term "heteroaryl" refers to a mono- or bicyclic

carbocyclic ring system having one or two aromatic rings containing from one to three heteroatoms and includes, but is not limited to, furyl, thienyl, pyridyl and the like.

The term "bicyclic" represents either an unsaturated or saturated stable 7- to 12-membered bridged or fused bicyclic carbon ring. The bicyclic ring may be attached at any carbon atom which affords a stable structure. The term includes, but is not limited to, naphthyl, dicyclohexyl, dicyclohexenyl, and the like.

As used herein, the term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water and emulsions such as an oil/water or water/oil emulsion, and various types of wetting agents.

As used herein, "effective amount" means an amount sufficient to produce a selected effect. For example, an effective amount of an anticonvulsant themisone derivative is an amount of the compound sufficient to reduce the incidence of seizures in a patient receiving the dose amount.

The term, "parenteral" means not through the alimentary canal but by some other route such as subcutaneous, intramuscular, intraspinal, or intravenous.

As used herein the term "neurological disease" or "neurological condition" includes neurological related maladies such as spasticity, seizures, depression or mood disorders, neuropathic pain, Alzheimer's Disease, Parkinson's Disease, HIV Dementia and neurological disorders that involve excessive activation of the N-methyl-D-aspartate (NMDA) receptor.

Compounds of the present invention that have one or more asymmetric carbon atoms may exist as the optically pure enantiomers, or optically pure diastereomers, as well as mixtures of enantiomers, mixtures of diastereomers, and racemic mixtures of such stereoisomers. The present invention includes within its scope all such isomers and mixtures thereof.

The MAC value is the minimum alveolar concentration of anesthetic at 1 atm that produces immobility in 50% of the subjects.

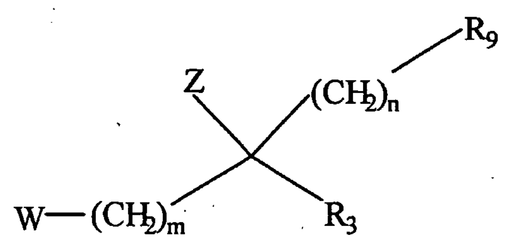
The Invention

Previously in the 1950's atrolactamide (themisone) was tested as an anticonvulsant. This compound was found to have anticonvulsant activity but was

toxic (blood dyscrasias, rash). Based on applicant's believe that the toxicity of these compounds derived from the formation of the metabolite 2-phenyl-acrylamide, the novel themisone-related compounds of the present invention were prepared that are blocked from the formation of 2-phenyl-acrylamide. With that in mind compound ICM-I-40N (**17**) was synthesized and evaluated for anticonvulsant activity.

The themisone derivatives of the present invention exhibit similar activities to themisone without the risk of the toxicities associated with themisone administration. Furthermore, applicants have discovered that the themisone derivatives of the present invention also have activity as anesthetics.

In accordance with one embodiment the novel themisone derivatives of the present invention have the general structure:



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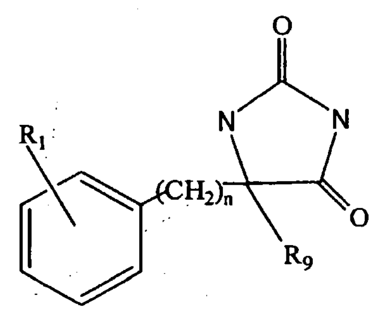


wherein W is selected from the group consisting of alkyl, alkenyl, alkynyl optionally substituted aryl, and optionally substituted heteroaryl;

Z is hydroxy, alkoxy, $-OCOR_{12}$, or, $-COR_{12}$;

R_1 is selected from the group consisting of H, halo, C_1-C_4 haloalkyl, $-NH_2$, hydroxy, and C_1-C_4 alkoxy;

R_3 is aryl, carboxyl, haloalkyl or -(C_1-C_4 alkyl)NHR_4, $-CONR_{10}R_4$ or H;

R_4 is selected from the group consisting of C_1-C_4 alkyl, aryl and H;

R_{10} is H or C_1-C_4 alkyl;

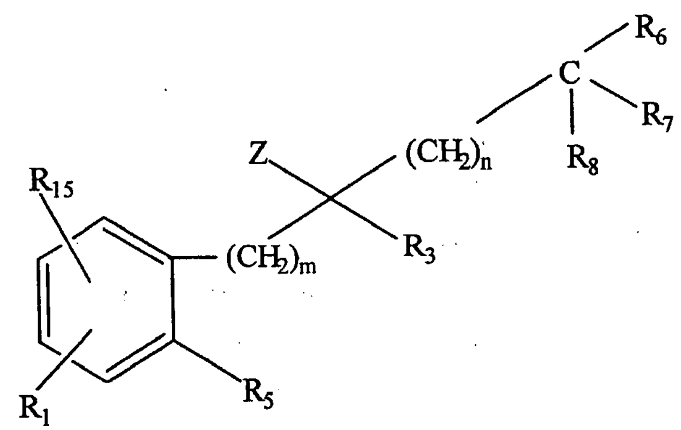
R_9 is optionally substituted aryl or haloalkyl;

R_{12} is C_1-C_4 alkyl, NH_2 or aryl;

m is an integer ranging from 0-3; and

n is an integer ranging from 0-1.

More particularly, the present invention is directed to a compound represented by a formula selected from the group consisting of:



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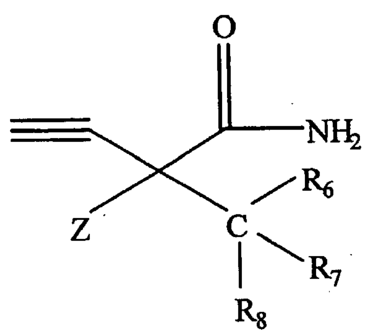

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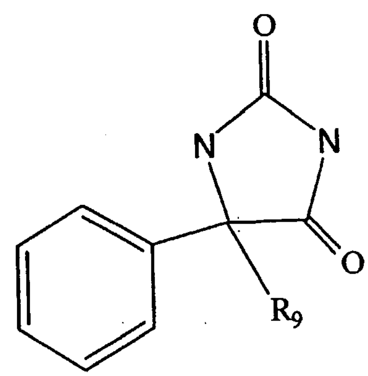


wherein R_1 and R_{15} are independently selected from the group consisting of H, halo, C_1-C_4 haloalkyl, $-NH_2$, hydroxy, and C_1-C_4 alkoxy;

Z is hydroxy or alkoxy;

R_3 is aryl, carboxyl, haloalkyl, -(C_1-C_4 alkyl)NHR_4, $-CONR_{10}R_4$ or H;

R_4 is selected from the group consisting of C_1-C_4 alkyl, aryl and H;

R_5 and R_{10} are independently H or C_1-C_4 alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

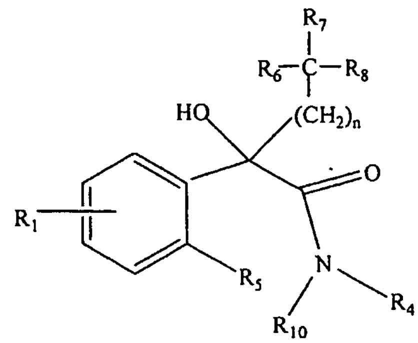
R_6, R_7 and R_8 are independently halo;

R_9 is optionally substituted aryl or haloalkyl;

m is an integer ranging from 0-1; and

n is an integer ranging from 0-1.

In accordance with one preferred embodiment the themisone derived compound has the general structure:



wherein R_1 is H or halo;

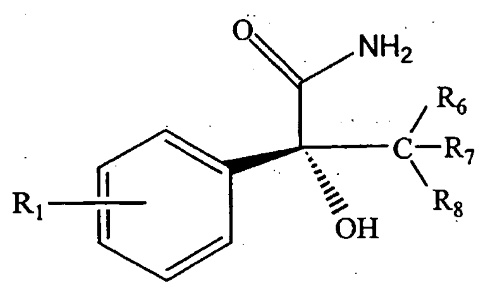
R_{10} and R_5 are independently H, C_1-C_4 alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

R_4 is selected from the group consisting of C_1-C_4 alkyl, aryl and H;

R_6, R_7 and R_8 are independently halo; and

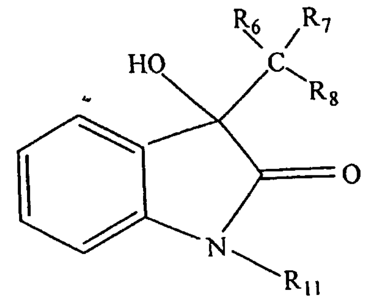
n is an integer ranging from 0-1. More preferably, R_1 is halo, R_{10}, R_4 and R_5 are H, n is 0; and R_6, R_7 and R_8 are independently selected from the group consisting of F, Cl and Br. In one preferred embodiment the R_1 substituent is in the meta or para position and R_6, R_7 and R_8 are each F.

In one embodiment the themisone derivative compound has the general structure:



wherein R_1 is H or halo; and R_6, R_7 and R_8 are independently selected from the group consisting of F, Cl and Br.

In an alternative embodiment, the themisone derived compound is represented by the formula



wherein R_{11} is selected from the group consisting of C_1-C_4 alkyl, aryl and H; and R_6, R_7 and R_8 are independently fluorine or chlorine. In one preferred embodiment, R_{11} is H or C_1-C_4 alkyl and R_6, R_7 and R_8 are each fluorine

In accordance with one embodiment the themisone derivatives of the present invention can be formulated as pharmaceutical compositions by combining the compounds with one or more pharmaceutically acceptable carriers, fillers, solubilizing agents and stabilizers known to those skilled in the art. Such pharmaceutical compositions can be utilized as analgesics, sedatives, anesthetics or as anticonvulsants.

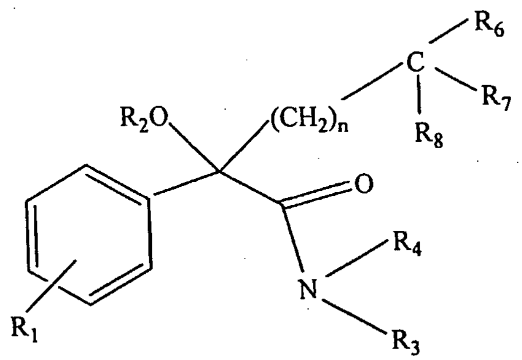
Pharmaceutical compositions comprising the themisone derivatives of the present invention are administered to an individual in need thereof by any number of routes including, but not limited to, topical, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means, with oral and intravenous routes being preferred. When administered orally, the compounds can be administered as a liquid solution, powder (lyophilized or otherwise), tablet, capsule or lozenge. Furthermore, oral formulations may include one or more of the present compounds in combination with one or more conventional pharmaceutical additive or excipients that are typically used in the preparation of tablets, capsules, lozenges and other orally administrable forms. When administered as an intravenous solution, the derivatives of the present invention can be admixed with conventional IV solutions to form injectable aqueous or oily suspensions or solutions.

In accordance with one embodiment, the themisone derivatives of the present invention are combined with other known anesthetic agents to enhance the performance of such compounds and decrease the incidence of negative side effects. For example, compositions according to the present invention may comprise a themisone derivative and phencyclidine type general anesthetic such as ketamine or tiletamine and their pharmaceutically acceptable salts, as well as selegiline or one of its pharmaceutically acceptable salts, combined in a single pharmaceutical composition for simultaneous administration, or presented separately for administration in close succession. In the latter case, selegiline has the role of pre-anesthetic or restraining agent. Tiletamine is 2-(ethylamino)-2-(2-thienyl)cyclohexanone. Ketamine is (+-)-2-(2-chlorophenyl)-2-methyl-aminocyclohexanone. Selegiline (-)-N, alpha-dimethyl-N-(2-propynyl) phenethylamine.

The present invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the themisone derivatives of the present invention. In accordance with one embodiment a kit is provided for anesthetizing a patient. In this embodiment the kit may comprise one or more anesthetic agents of the present invention and as well as other known anesthetic agents and pre-anesthetic or restraining agents. These pharmaceuticals can be packaged in a variety of containers, *e.g.*, vials, tubes, microtiter well plates, bottles, and the like. Preferably, the kits will also include instructions for use.

In one embodiment a composition comprising a themisone derivative of the present invention is used as a general anesthesia in mammals, including both human and domesticated animals. More particularly, compositions comprising the present themisone derivative are administered either orally or parenterally to a mammalian species to induce anesthesia. When administered orally, the compounds are administered as a liquid solution, powder, tablet, capsule or lozenge. The compounds can be used in combination with one or more conventional pharmaceutical additive or excipients used in the preparation of tablets, capsules, lozenges and other orally administrable forms. When administered parenterally, and more preferably by intravenous injection, the derivatives of the present invention can be admixed with saline solutions and/or conventional IV solutions.

In accordance with one embodiment, a method is provided for inducing anesthesia in a human patient. The method comprises the steps of administering to the patient a composition comprising a compound represented by a formula selected from the group consisting of



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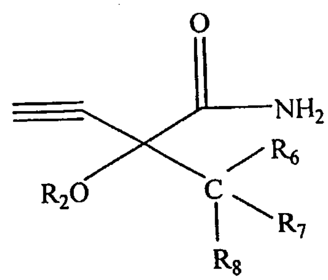


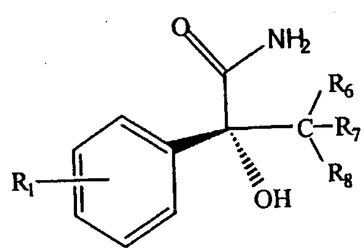
wherein R_1 is selected from the group consisting of H, halo, C_1-C_4 haloalkyl, -NH_2, hydroxy, and C_1-C_4 alkoxy;

R_2, R_3 and R_4 are independently H or alkyl;

R_6, R_7 and R_8 are independently halo; and

n is an integer ranging from 0-4, and a pharmaceutically acceptable carrier.

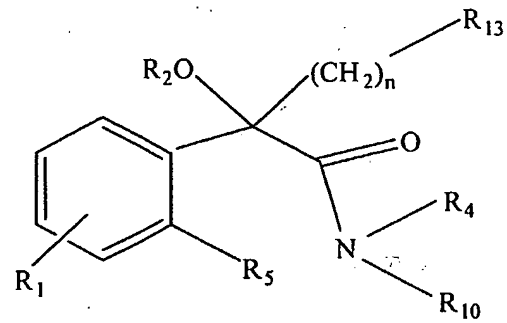
In one preferred embodiment the method of inducing anesthesia in a mammalian species comprising administering a pharmaceutical composition comprising a compound of the general formula:

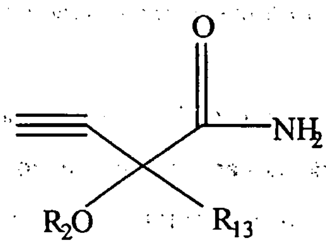


wherein R_1 is selected from the group consisting of H or halo and R_6, R_7 and R_8 are independently H or halo, with the proviso that at least one and more preferably two of R_6, R_7 and R_8 are halo. More preferably R_1 is F or Br and R_6, R_7 and R_8 are independently F or Cl.

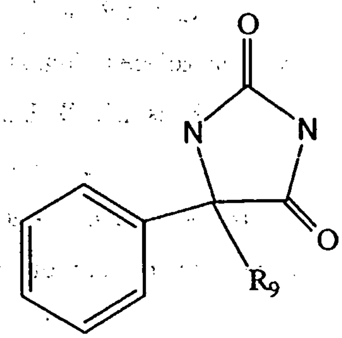
In accordance with one embodiment, a method is provided for treating a neurological condition, including the treatment of seizures. The method comprises

the steps of administering to a patient a composition comprising a compound represented by a formula selected from the group consisting of





and



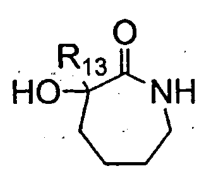
wherein R_1 is selected from the group consisting of H, halo, C_1-C_4 haloalkyl, $-NH_2$, hydroxy, and C_1-C_4 alkoxy;

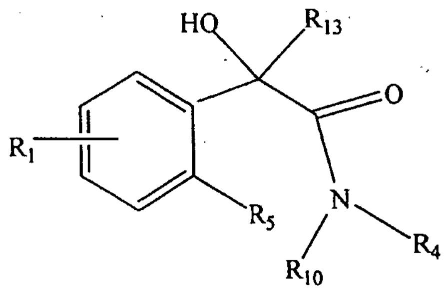
R_2 and R_4 are independently H or alkyl;

R_{10} and R_5 are independently H, alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

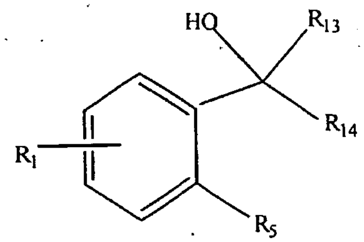
R_9 is optionally substituted aryl or haloalkyl; n is an integer ranging from 0-2; and R_{13} is haloalkyl. More preferably, R_1 is H or halo, R_2 is H and n is 0.

In accordance with one embodiment the method of treating a neurological condition comprises administering a composition comprising a compound of the general formula:





or



wherein R_1 is H or halo;

R_4 is H or alkyl;

R_{10} and R_5 are independently H, alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

R_{13} is haloalkyl; and

R_{14} is C_1-C_{12} alkyl. More preferably, R_1 is H or halo, R_4, R_5 and R_{10} are H and R_{14} is C_4-C_6 alkyl. In one embodiment these compounds are administered to a patient as a treatment for reducing the incidence and severity of seizures.

In accordance with the present invention compositions comprising an atrolactamide derivative are administered to a patient to provide neuroprotection in systemic and neurological disease, including neuropathic pain. The compounds can be administered prophylactically, acutely, subacutely, or chronically via the intravenous, oral or rectal route. The compounds of the present invention are anticipated to have activity as analgesics, anti-arrhythmics, mood stabilizers, neuroprotectants and inhibitors of prostate cancer.

In accordance with one embodiment, the hydrogens of the 2-methyl group substituent of themisone are substituted with halo groups to prevent the elimination reaction and formation of 2-phenyl-acrylamide. For example, the hydrogens can be replaced with fluorine to create 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide **(17)**. Fluorine is an classic mimic for hydrogen, with the two elements having similar Van der Waals radii, 1.20 and 1.35 angstroms, respectively.

Anticonvulsant testing of 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide **(17)** in rats revealed the compounds have anesthetic activity at an oral ED_{50} of 9 mg/kg and toxicity at 300 mg/kg. Further testing in UVa's Department of Anesthesiology revealed the fluorinated derivative lowered the minimum alveolar

concentration (MAC) value of isoflurane (1.2% in O_2) by sixty percent, with no hemodynamic effects. Furthermore, testing of 3,3,3-Trifluoro-2-hydroxy-2-(4-fluoro-phenyl)-propionamide **(39)** revealed this compound provided 3 out of 4 animals with a 100% reduction in Isoflurane MAC at 300mg/kg. The tested animals exhibited surgical anesthesia, the third stage of anesthesia displayed by general loss of spinal reflexes and muscle tone. Themisone was later tested and found to have no anesthetic activity. Other themisone compounds have now been tested and found to exhibit both anticonvulsant and anesthetic activities as described in the following examples.

Compound **39** also demonstrated activity as an anticonvulsant both in the MES and scMET assays (See Example 3). In particular, in phase I oral rat data generated with MES, 4 out of 4 rats were protected using 30mg/kg for a duration of 2 hours. In phase I intraparentoneal data for MES 2 out of 3 mice were protected at 100 mg/kg for a duration of 1 hour and 5out of 5 mice were protected at 100mg/kg for a duration of 0.5 hours. Neurotoxicity revealed that seven of eight mice were unable to grasp rod at 100 mg/kg for a duration of 0.5 hours.

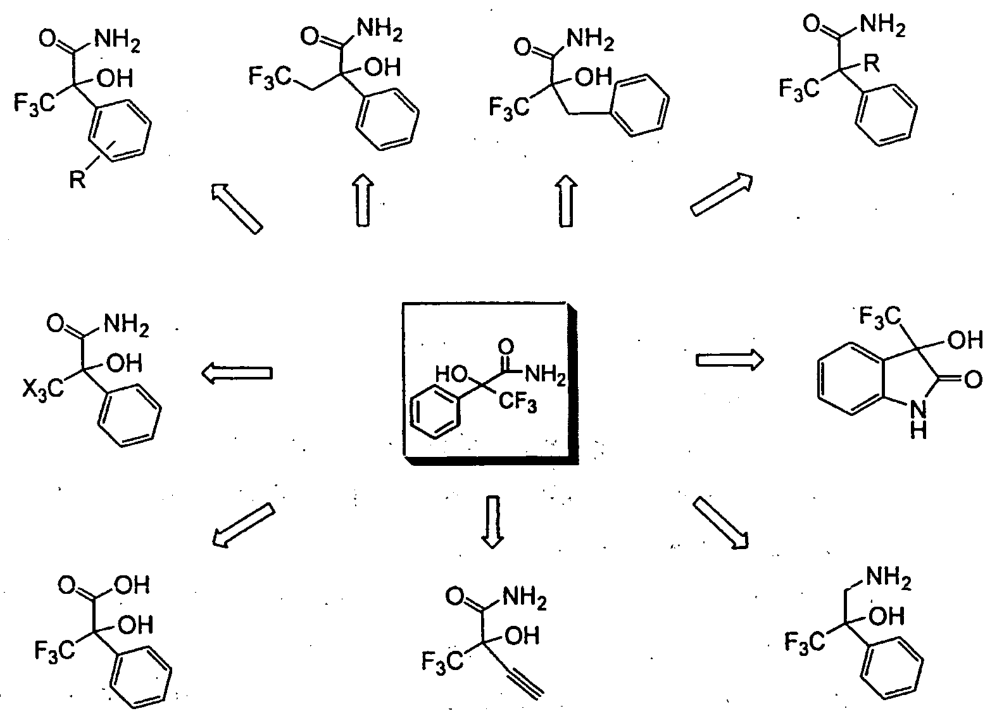
Example 1

Structure Activity Relationship (SAR) of 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide Using Ligand Based Design

In accordance with one embodiment of the present invention, the formation of 2-phenyl-acrylamide is blocked by replacing the hydrogens of the 2-methyl group substituent of themisone with compounds that prevent the elimination reaction. For example, the hydrogens can be replaced with fluorine to create 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide **(17)**.

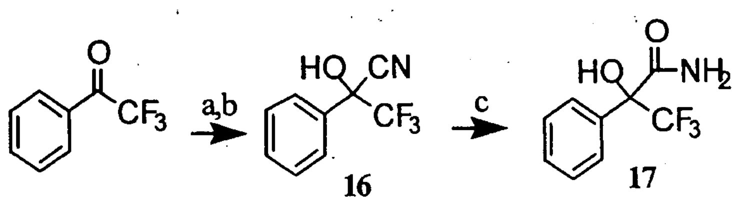
Anticonvulsant testing of 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide **(17)** in rats revealed that in addition to exhibiting anticonvulsant activity, this themisone derivative has anesthetic activity at an oral ED_{50} of 9 mg/kg and toxicity at 300 mg/kg. Themisone was later tested and found to have no anesthetic activity. Animals administered 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide **(17)** exhibited surgical anesthesia, the third stage of anesthesia displayed by general loss of spinal reflexes and muscle tone. Further testing in UVa's Department of Anesthesiology revealed the fluorinated derivative lowered the minimum alveolar concentration (MAC) value of isoflurane (1.2% in O_2) by sixty percent, with no hemodynamic effects. In general for compound **17** investigation of structure to general anesthetic relationship revealed that the phenyl ring conformation of **17** is important and that para-electron withdrawing groups increase the anesthetic activity of the compound. In addition increased halogen size and saturation at the position 3 carbon also increase anesthetic activity. A hydrogen bond donor is also important at the position 2 carbon, but bulk is not well tolerated.

To investigate the activity of various 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide related compounds, the following derivative compounds will be prepared:



It is anticipated that these derivatives will provide an orally available general anesthetic that is capable of inducing anesthesia smoothly and rapidly, allow rapid recovery, and pose a wide margin of safety (high therapeutic index). These compounds are also expected to exhibit dual anticonvulsant activity. Synthesis of the dual anticonvulsants and general anesthetics began with the hydroxyamides of the commerically available phenyl substituted trifluoro-methyl ketones.

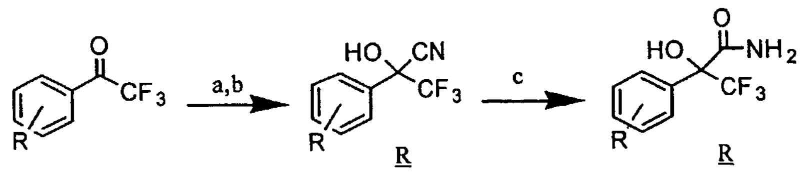
Scheme I



Reaction conditions: **a**: TMSCN,$TiCl_4$, CH_2Cl_2; **b**: H_2O; **c**: 1,4-dioxane, conc. HCl, HCl gas.

Similarly, the synthetic scheme for preparing *meta*-F, *para*-Cl derivatives is shown in scheme II, respectively:

Scheme II



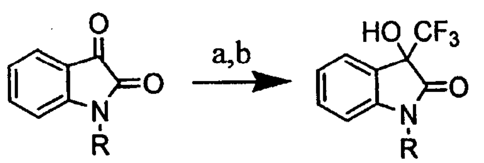
R
18 m-F
19 p-Cl

R
20 m-F
21 p-C

Reaction conditions: **a**: TMSCN,ZnI_2, CH_2Cl_2; **b**: 15% HCl, THF; **c**: 1,4-dioxane, conc. HCl, HCl gas.

Closed ring analogs of the lead compound were synthesized by the use of TMS-CF_3 (see Scheme III). Several attempts had been made to synthesize the compound with the use of tetrabutylammonium fluoride (TBAF). The trimethylsilyl ether intermediate was found to be very stable and difficult to quench with varying amounts of acid. The exothermic reaction of a catalytic amount of KF, and saturated t-BuOK in THF, was found to produce the desired product, although in low yield with unprotected amides.

Scheme III

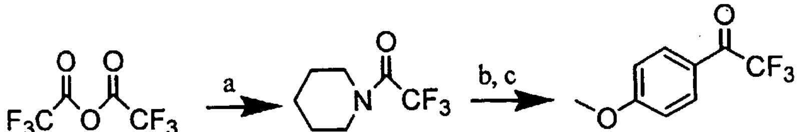


R
22 -H
23 -Me
24 -Ph

Reaction Conditions: **a**: TMS-CF3, KF, t-BuOK, THF; **b**: 15% HCl

N-trifluoroacetylpiperdine **25** was reacted with 0.8 equivalents of 4-Bromoanisole to yield **26** (see Scheme IV). All other ketones can now be synthesized to yield all the remaining hydroxyamides with the use of TMS-CN, followed by HCl gas.

Scheme IV



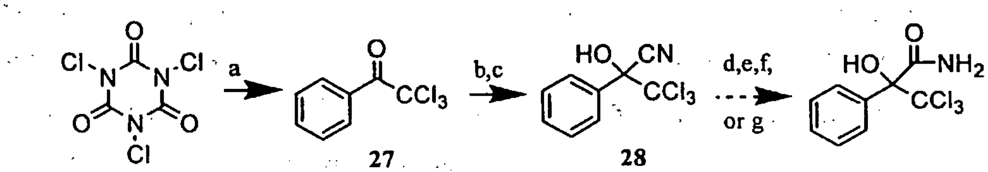
25

26

Rxn Conditions: **a**: piperdine, Et_3N, Ether; **b**: 4-Bromoanisole, Mg, I_2, THF; **c**: NH_4Cl

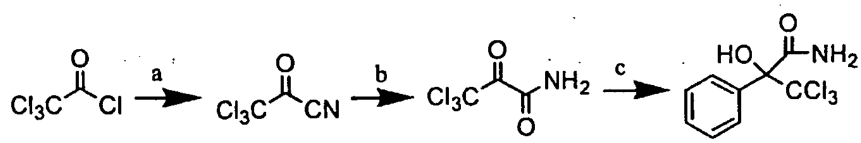
Halogenation of general anesthetics stabilizes the compounds and reduces metabolism. We hypothesized that changes in the haloform content could have an affect on potency, duration and hemodynamic acitivty. The chlorinated cyanohydrin **28** was successfully made (see Scheme V), although several attempts to synthesize the hydroxyamide were unsuccessful. Under acidic conditions such as HCl and HCl gas, or formic acid and HCl gas converted the cyanohydrin back to the starting ketone. Other unsuccessful attempts included K_2CO_3 and 30% H_2O_2, and UHP and K_2CO_3. A new synthetic scheme is now being evaluated starting with the acid chloride, trichloroacetyl chloride (see Scheme VI). The brominated ketone was made, although in low yield (see Scheme VII). Several attempts to form the cyanohydrin, with the use of TMS-CN and various catalysts were unsuccessful. It is believed that steric hinderance plays a large role in the difficulty of synthesizing these two hydroxyamides.

Scheme V



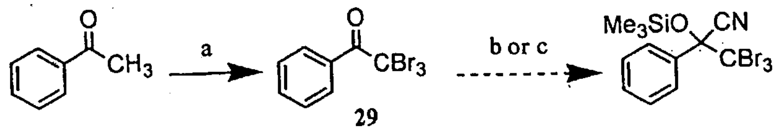
Reaction Conditions: **a**: acetophenone, acetic acid, reflux, 8 hrs.; **b**: TMS-CN, THF, reflux, 12 hrs.; **c**: 15% HCl; **d**: conc. HCl, HCl gas; **e**: formic acid, HCl gas; **f**: K_2CO_3, 30% H_2O_2; **g**: UHP, K_2CO_3.

Scheme VI



Reaction Conditions: **a**: KCN, 18-crown-6, CH_2Cl_2; **b**: DMSO, K_2CO_3, 30% H_2O_2; **c**: $ZnPh_2$

Scheme VII



29

Reaction Conditions: **a**: Br_2, NaOH, H_2O, 1,4-dioxane, 0°C to RT; **b**: TMS-CN, ZnI_2, CH_2Cl_2; **c**: TMS-CN, KCN, 18-crown-6, CH_2Cl_2.

200 mg of each compound are tested for general anesthesia activity. Testing is performed on rats to determine the percent reduction in the use of isoflurane. Inhaled anesthetics still need to be utilized to rapidly adjust the level of anesthesia. Since no single anesthetic is capable of all four requirements for anesthesia, a combination is utilized. The rats were first anesthesized with isoflurane, intubated, ventilated and then a femoral line was inserted. After the rat had been stable for 15 minutes, the initial minimum alveolar concentration (MAC) value was determined. Then, 60 mg/kg of drug was sonicated in 3 mL of peanut oil and injected (i.p.). After 30 minutes the second MAC value was determined post administration. Finally, after one hour the third MAC value was determined. At each MAC determination, a sample of blood was taken to determine pH, pCO_2, and pO_2. The results of the compounds tested to date are compared to the lead compound **17**.

A classical comparison of log P and MAC reduction was investigated. A graph representing the effects of log P on the biological activity is presented in graphic form (See Fig 1). The general anesthetic activity of compounds **20-23** and **36-43** were compared to lead compound **17** as represented in the graph (Fig. 1) and in Table 1. The partition coefficient, P, is a measure of the way the compound distributes itself between octanol and water. The graph displays a general parabola shape with an optimal log P value of approximately 1.5, since compounds **20** and **42** were very toxic, despite their high activity. Compounds **20** and **42** also had a low lethal dose of 300 mg/kg. Derivatives with para- substituted phenol ring derivatives **21** and **39** were found to be very active, but also toxic at the same dosage. Therefore, meta-substituted derivatives **20** will be the focus of future synthesize. Bulky substituents on the alcohol were also found to have low activity. Closed ring analogs are active at lower levels but cause no hemodynamic effects.

Table 1:

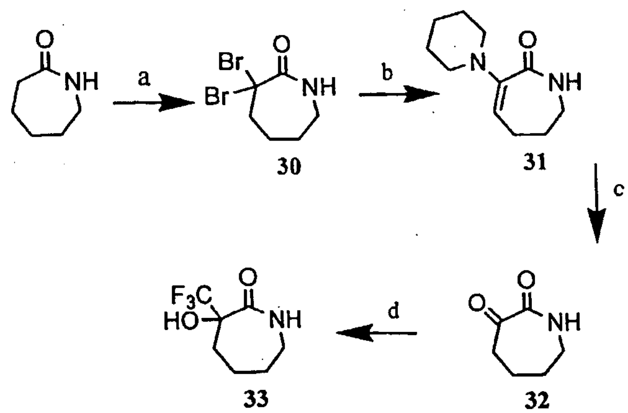
Compound	MAC value of Isoflurane at 60mg/kg of compound*	Percent Reduction in Isoflurane	Hemodynamic Effects	Log P
17	0.65	46	none	1.26
20	0.70	42	lowers blood pressure	1.82
21	0.65	46	none	1.42
22	1.05	12.5	none	1.13
23	0.95	20.8	none	1.36

* 1.2 % isoflurane generates 100% anesthesia; log P calculated using by Crippen's fragmentation: J.Chem.Inf.Comput.Sci.,27,21(1987) in ChemDraw Ultra

Example 2

The phenyl-substituted caprolactams have been found to be very active anticonvulsants. Therefore, the $-CF_3$ moiety was added to the seven membered ring carpolactam (see Scheme VIII) and these compounds are anticipated to have activity as anticonvulsants. -Caprolactam is alpha brominated with bromine and phosphorus pentachloride. Formation of the enamine **31** is accomplished with **30** refluxed in piperdine for 6 hours. Cleavage of the enamine is done on a silica gel column eluted with ethyl acetate. Due to the low yield of **32** the amide was protected before the reaction with TMS-CF_3. There were several unsuccessful attempts to protect the amide, using benzyl bromide and various bases.

Scheme VIII



30 31 33 32

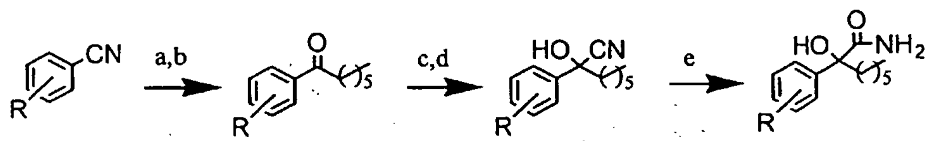
Reaction Conditions: **a**:Br_2, PCl_5, $CHCl_3$; **b**: piperdine, reflux, 6 hrs.; **c**: silica gel, EtOAc; **d**: TMS-CF_3.

Example 3

Anticonvulsant Properties of the Themisone Derivative Compounds

To investigate the anticonvulsant properties of the themisone derivatives, synthesis of the seven chain carbon hydroxyamides with substituted chlorine and methoxy groups on the phenyl ring were prepared in accordance with scheme IX. These derivatives were made as anticonvulsants and were not predicted to be active general anesthetics.

Scheme IX



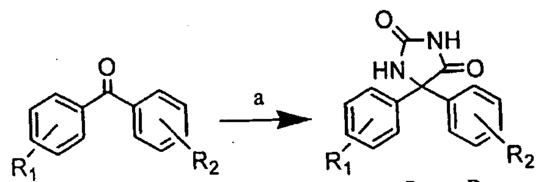
R	R	R
1 o- Cl	**6** o- Cl	**11** o- Cl
2 m-Cl	**7** m-Cl	**12** m-Cl
3 o-OMe	**8** o-OMe	**13** o-OMe
4 m-OMe	**9** m-OMe	**14** m-OMe
5 p-OMe	**10** p-OMe	**15** p-OMe

Reaction Conditions: **a**: 1-Bromoheptane, Mg, I_2, THF; **b**: 15% HCl; **c**: TMSCN, ZnI_2, CH_2Cl_2; **d**: 15% HCl, THF; **e**: 1,4 - dioxane, conc. HCl, HCl gas.

300 mg of each compound was synthesized and sent to the National Institute of Health's Anticonvulsant Screening Project of the Antiepileptic Drug Discovery Program. NIH performs anticonvulsant testing (oral and intraperitoneal, i.p.) on both mice and rats in phase I trials. The grand mal model is conducted with a maximal electroshock (MES) test, where corneal electrode implants are primed with a drop of electrolyte solution and an electrical stimulus is delivered for 0.2 second. The model examines the compounds' ability to stop the spread of seizures. The petite mal model is conducted with a subcutaneous pentylenetetrazol seizure threshold (scMet) test. The animals are injected with a convulsant dose of pentylenetetrazol at the peak effect time of the compound. This model measures the compounds' threshold for seizures. A toxicity test (TOX) is performed where the animals walk on a spinning rod for varying lengths of time to check for the loss of righting reflex or other toxic effects. Phase I evaluation at 30, 100 and 300 mg/kg of test compounds has resulted in several newly discovered active anticonvulsants (See Figs. 2-5).

One important aspect of central nervous system drug delivery is brain distribution. Derivatives of phenytoin were designed and synthesized with fluorine tags (see scheme IX). The compounds were tested using the kindling model to access their anticonvulsant activity. Rats with the injected drugs will then be exposed to ^{19}F magnetic resonance imaging (MRI) to study the drug distribution in the brain of a known compound. The model will then be used as a model to test the active fluorinated compounds.

Scheme X



	R_1	R_2
34	-F	-H
35	-F	-F

Reaction Conditions: a: KCN, (NH4)2CO3, 50 % EtOH, 65°C, 24 hrs.

Table 2: Anticonvulsant Testing (NIH)

Mice I.P. Administration

		Cmp 20	Cmp 20	Cmp 21	Cmp 21	Cmp 23	Cmp 23
Test	**Dose (mg/ kg)**	*Time (0.5 hours)*	*Time (4.0 hours)*	*Time (0.5 hours)*	*Time (4.0 hours)*	*Time (0.5 hours)*	*Time (4.0 hours)*
MES	**30**	0/1[a]	0/1	0/1	0/1	0/1	0/1
MES	**100**	3/3	3/3	0/3	1/3	3/3	0/3
MES	**300**	0/0	1/1	n/a	n/a	1/1	1/1
SCMET	**30**	2/5	0/1	0/1	0/1	1/5	0/1
SCMET	**100**	1/1	1/1	4/4	1/1	0/1	0/1
SCMET	**300**	n/a	n/a	0/0	1/1	1/1	1/1
TOX	**30**	0/4	0/2	0/4	0/2	0/4	0/2
TOX	**100**	6/8	0/4	6/8	3/4	1/8	0/4
TOX	**300**	4/4[b]	1/1[c]	4/4[b]	1/1[c]	4/4[c]	1/2

a: 0/1 refers to number of animals protected/ number of animals tested

b: loss of righting reflex and one death

c: loss of righting reflex

Table 3: Anticonvulsant Testing (NIH)

Rat Oral Administration- Compound 21

Test	**Dose (mg/kg)**	*0.25 hrs.*	*0.5 hrs.*	*1.0 hrs.*	*2.0 hrs.*	*4.0 hrs.*
MES	**30**	1/4	1/4	1/4	1/4	1/4
TOX	**30**	0/4	0/4	0/4	0/4	0/4

Table 4: Anticonvulsant Testing (NIH)

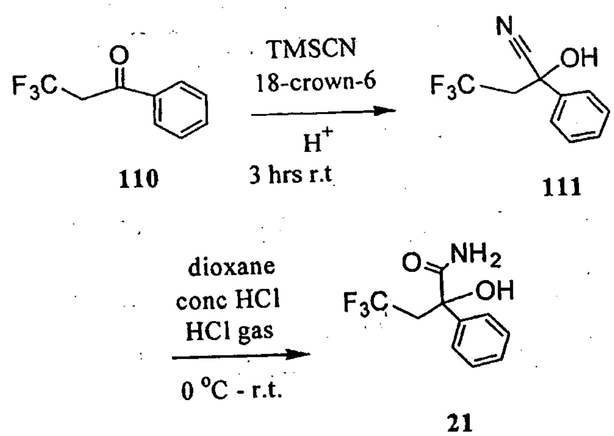
Rat Oral Administration- Compound 23

Test	**Dose (mg/kg)**	*0.25 hrs.*	*0.5 hrs.*	*1.0 hrs.*	*2.0 hrs.*	*4.0 hrs.*
MES	**30**	2/4	1/4	2/4	2/4	2/4
TOX	**30**	0/4	0/4	0/4	0/4	0/4

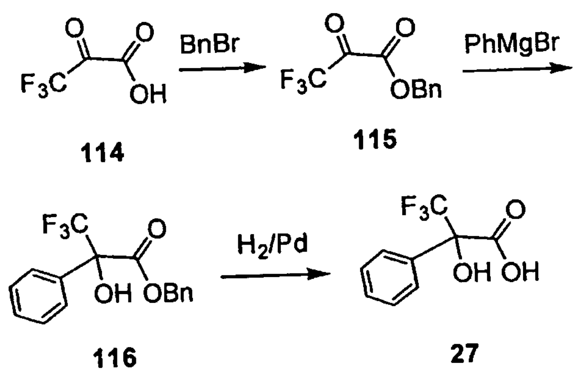
Example 4

Additional Synthetic Schemes

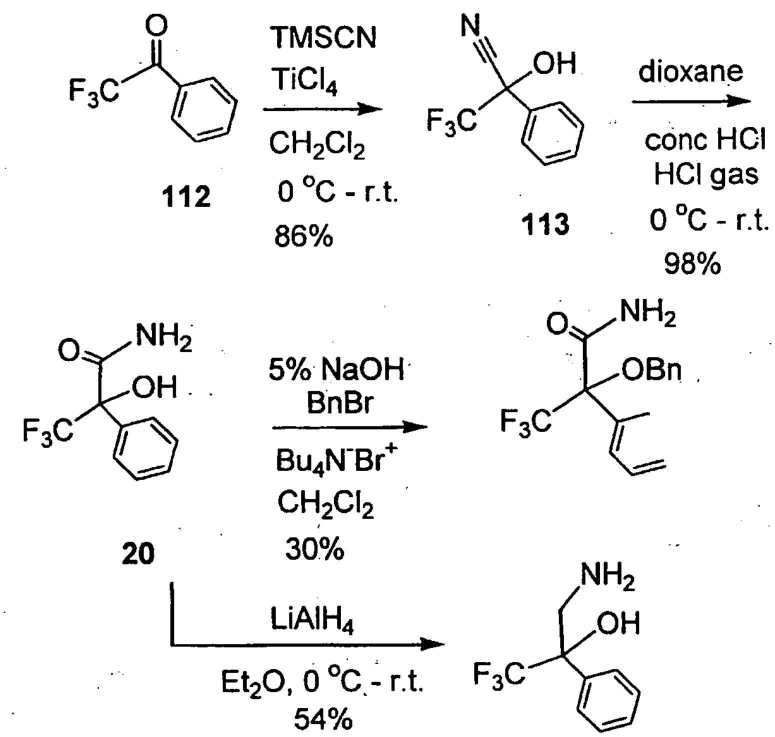
Scheme XI



Scheme XII

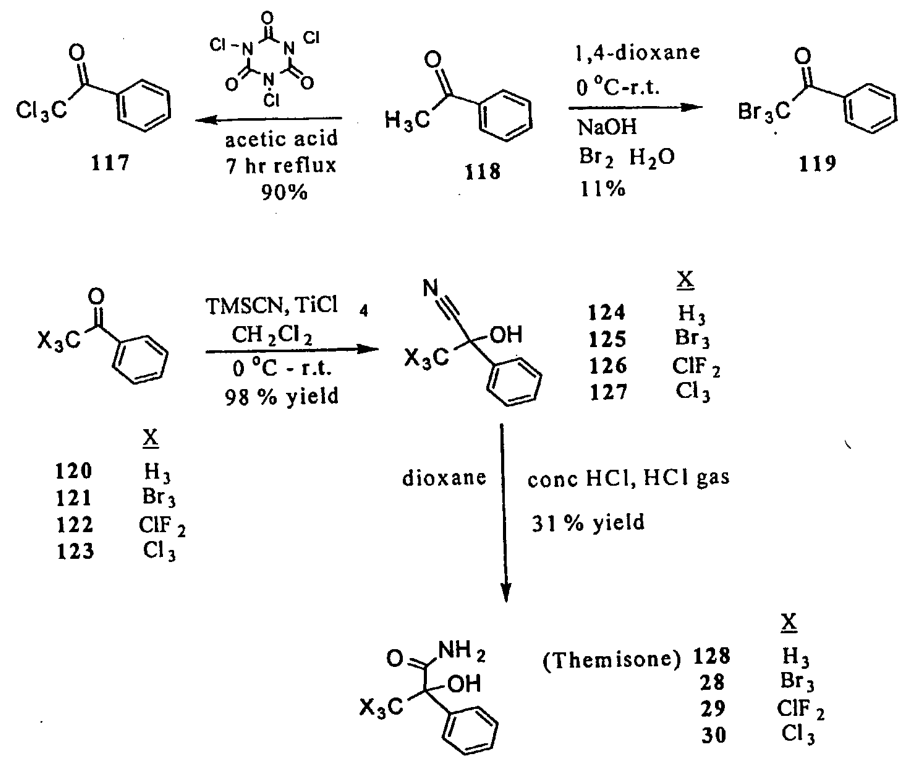


Scheme XIII



O
F_3C
112
TMSCN
$TiCl_4$
CH_2Cl_2
0 °C - r.t.
86%
N
OH
F_3C
113
dioxane
conc HCl
HCl gas
0 °C - r.t.
98%
NH_2
O
OH
F_3C
20
5% NaOH
BnBr
$Bu_4N^-Br^+$
CH_2Cl_2
30%
O
NH_2
OBn
F_3C
$LiAlH_4$
Et_2O, 0 °C - r.t.
54%
NH_2
OH
F_3C

Scheme XIV

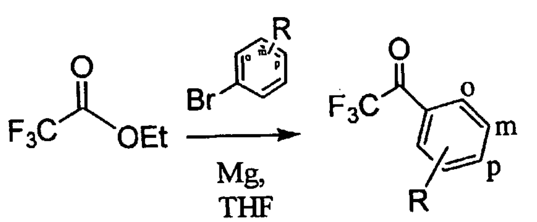


	X
120	H_3
121	Br_3
122	ClF_2
123	Cl_3

	X
124	H_3
125	Br_3
126	ClF_2
127	Cl_3

	X
(Themisone) 128	H_3
28	Br_3
29	ClF_2
30	Cl_3

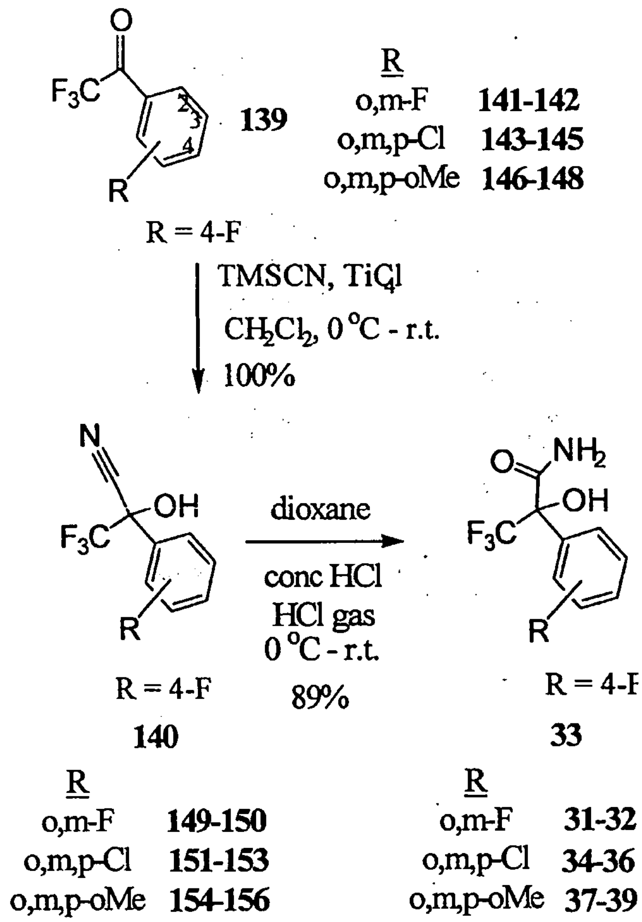
Scheme XV



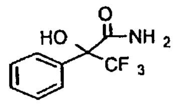
129

R	
o,m,p-F	**130-132**
o,m,p-Cl	**133-135**
o,m,p-oMe	**136-138**

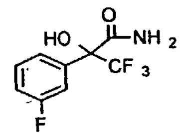
Scheme XVI


139
R
o,m-F 141-142
o,m,p-Cl 143-145
o,m,p-oMe 146-148
R = 4-F
TMSCN, TiCl4
CH2Cl2, 0 °C - r.t.
100%
dioxane
conc HCl
HCl gas
0 °C - r.t.
89%
R = 4-F
140
R = 4-F
33
R
o,m-F 149-150
o,m,p-Cl 151-153
o,m,p-oMe 154-156
R
o,m-F 31-32
o,m,p-Cl 34-36
o,m,p-oMe 37-39

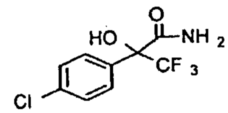
Synthesized themisone derivatives:



ICM-I-40N



20



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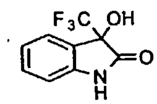

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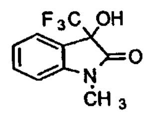

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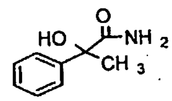
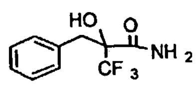


Themisone



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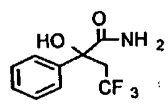
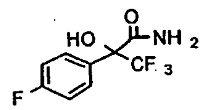
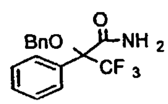


38



39



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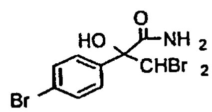

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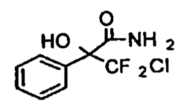

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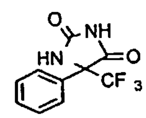
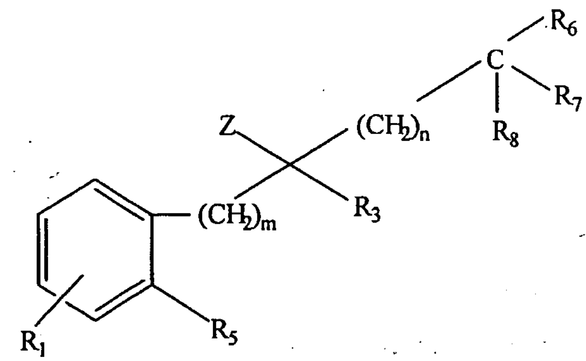
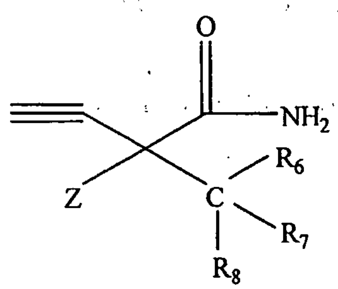


43

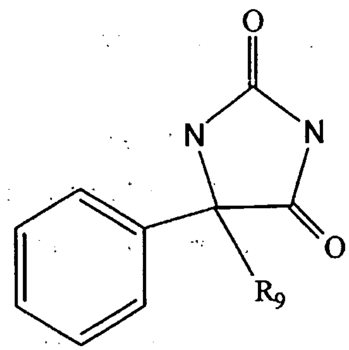
Claims:

1. A compound represented by a formula selected from the group consisting of





and



represented by a formula selected from the group consisting of wherein R_1 is selected from the group consisting of H, halo, and C_1-C_4 alkoxy;

Z is hydroxy, NH_2, alkoxy, $-OCOR_{12}$, or, $-COR_{12}$;

R_3 is aryl, carboxyl, haloalkyl or $-(C_1$-C_4 alkyl)NHR_4, $-CONR_{10}R_4$ or H;

R_4 is selected from the group consisting of C_1-C_4 alkyl, aryl and H;

R_5 and R_{10} are independently H or C_1-C_4 alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

R_6, R_7 and R_8 are independently halo;

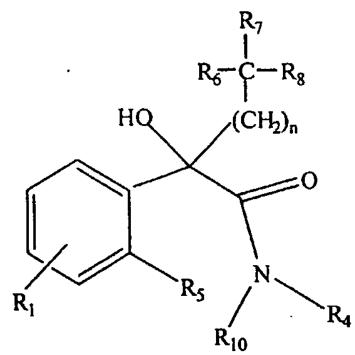
R_9 is optionally substituted aryl or haloalkyl;

R_{12} is H, C_1-C_4 alkyl or NH_2;

m is an integer ranging from 0-1; and

n is an integer ranging from 0-1.

2. The compound of claim 1, wherein the compound is represented by the formula:



wherein R_1 is H or halo;

R_{10} and R_5 are independently H, C_1-C_4 alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

R_4 is selected from the group consisting of C_1-C_4 alkyl, aryl and H;

R_6, R_7 and R_8 are independently halo; and

n is an integer ranging from 0-1.

3. The compound of claim 2 wherein

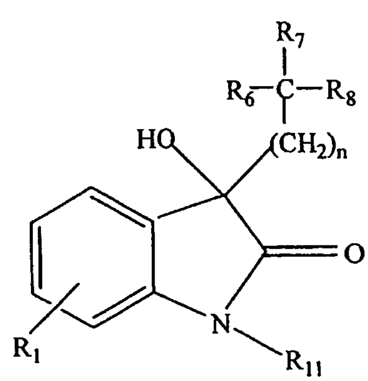
wherein R_1 is halo;

R_3, R_4 and R_5 are H;

n is 0; and

R_6, R_7 and R_8 are independently halo.

4. The compound of claim 1 wherein the compound is represented by the formula:



wherein R_1 is H;

R_{11} is selected from the group consisting of C_1-C_4 alkyl, aryl and H;

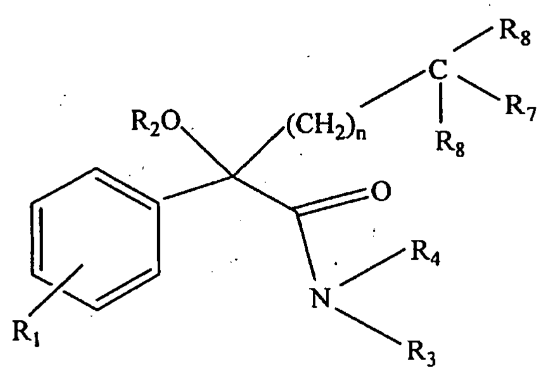
n is 0; and

R_6, R_7 and R_8 are independently halo.

5. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

6. The composition of claim 5 further comprising selegiline

7. A method for inducing anesthesia in a mammalian species said method comprising the steps of administering a composition comprising a compound represented by the formula:



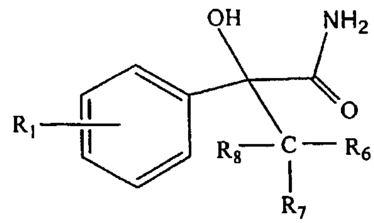
wherein R_1 is selected from the group consisting of H, halo, C_1-C_4 haloalkyl, $-NH_2$, hydroxy, and C_1-C_4 alkoxy;

R_2, R_3 and R_4 are independently H or alkyl;

R_6, R_7 and R_8 are independently halo; and

n is an integer ranging from 0-4 and a pharmaceutically acceptable carrier.

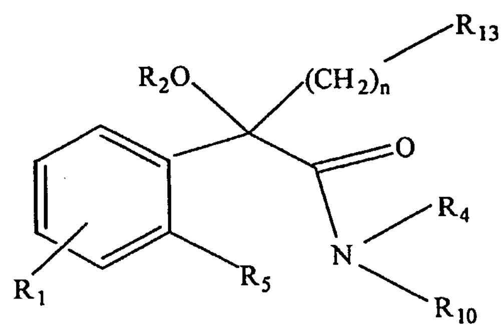
8. The method of claim 7 wherein said compound has the general structure:

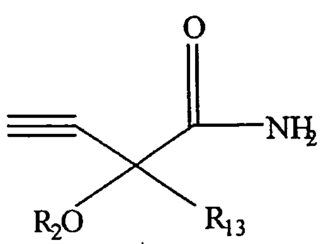


wherein R_1 is H or halo; and

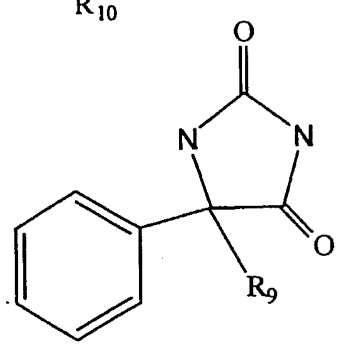
R_6, R_7 and R_8 are independently selected from the group consisting of F, Cl and Br.

9. A method for treating a neurological condition said method comprising the steps of administering a composition comprising a compound represented by the formula:





or



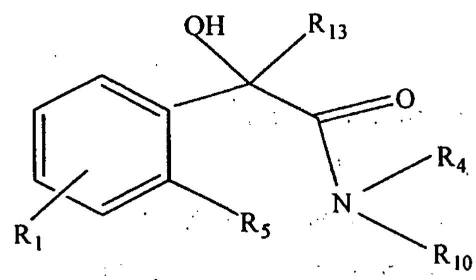
wherein R_1 is selected from the group consisting of H, halo, C_1-C_4 haloalkyl, -NH_2, hydroxy, and C_1-C_4 alkoxy;

R_2 and R_4 are independently H or alkyl;

R_{10} and R_5 are independently H, alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

R_9 is optionally substituted aryl or haloalkyl; n is an integer ranging from 0-2; and R_{13} is haloalkyl.

10. The method of claim 9 wherein the compound has the general structure



wherein R_1 is selected from the group consisting of H or halo;

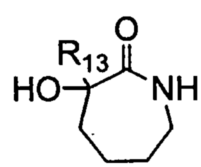
R_4 is H or alkyl;

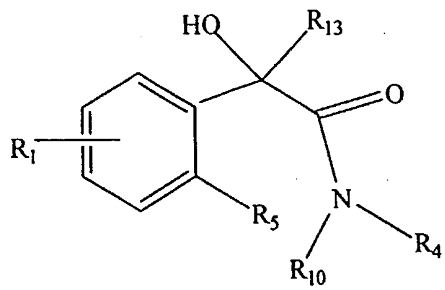
R_{10} and R_5 are independently H, alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

and R_{13} is haloalkyl.

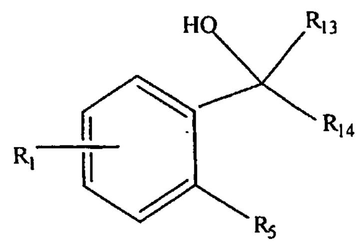
11. The method of claim 9 were the neurological condition to be treated is a seizure.

12. A method for treating a neurological condition said method comprising the steps of administering a composition comprising a compound represented by the formula:





or



wherein R_1 is H or halo;

R_4 is H or alkyl;

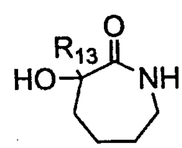
R_{10} and R_5 are independently H, alkyl, or R_{10} and R_5 taken together, can form with the adjacent ring, an optionally substituted 5- or 6-membered heterocyclic ring;

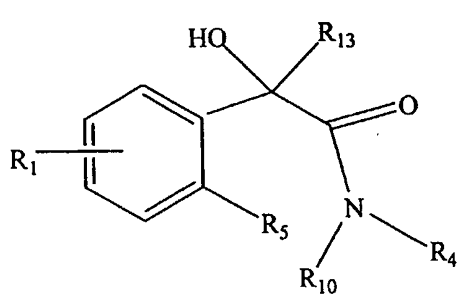
R_{13} is haloalkyl; and

R_{14} is C_1-C_{12} alkyl.

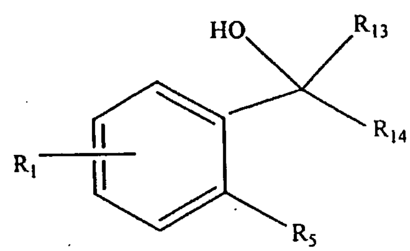
13. The method of claim 12 wherein R_1 is H or halo, R_4, R_5 and R_{10} are H and R_{14} is C_4-C_6 alkyl.

14. A compound represented by a formula selected from the group consisting of





and



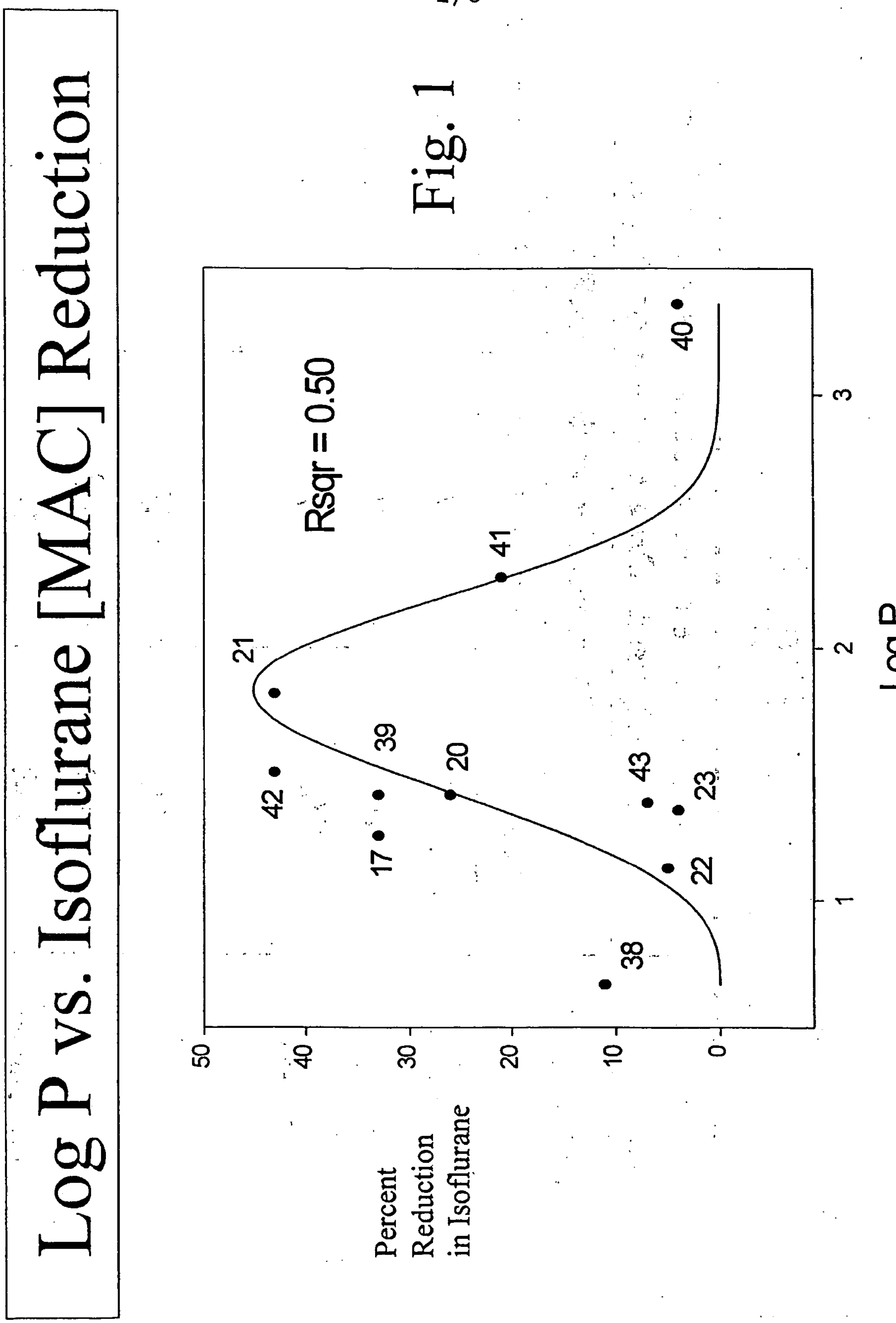

Log P vs. Isoflurane [MAC] Reduction
Rsqr = 0.50
21
41
40
42
39
20
17
43
23
22
38
50
40
30
20
10
0
1
2
3
Log P
Percent
Reduction
in Isoflurane

Fig. 1

Fig. 2

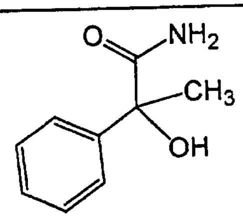
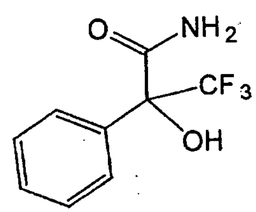
Phase I mouse data ***i.p.***	National Institute of Neurological Diseases and Stroke ***Anti-Epileptic Drug Development Program***		
	Maximal electroshock (MES)		
	Dose (mg/kg)	*Protected animals*	*Duration of action (hrs)*
 **Themisone**	30	0/1	-
	100	2/3	0.25
	300	1/1	0.5
 **ICM-I-40N(17)**	30	0/1	-
	100	**3/3**	**4**
	300	1/1	4

Fig. 3

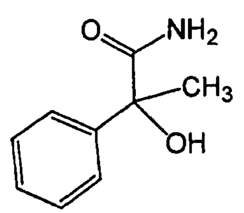
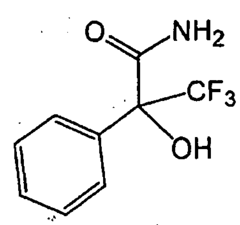
Phase I mouse data ***i.p.***	National Institute of Neurological Diseases and Stroke ***Anti-Epileptic Drug Development Program***		
	Subcutaneous Metrazol (scMet)		
	Dose (mg/kg)	*Protected animals*	*Duration of action (hrs)*
 **Themisone**	30	0/1	-
	100	5/5	0.25
	300	1/1	0.5
 **ICM-I-40N**	30	0/1	-
	100	**5/5**	**0.5**
	300	1/1	4

Fig. 4

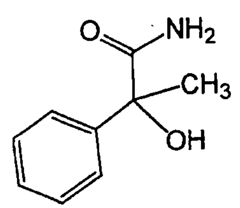
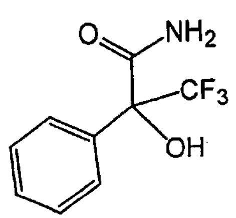
Phase I mouse data ***i.p.***	National Institute of Neurological Diseases and Stroke ***Anti-Epileptic Drug Development Program***		
	Rotorod neurotoxicity		
	Dose (mg/kg)	*Affected animals*	*Duration of toxicity (special comments)*
 **Themisone**	30 100 300	0/4 4/8 1/1	- 0.25 hrs 0.5 hrs
 **ICM-I-40N**	30 **100** 300 300	0/4 **2/4** 4/4 2/2	- 4 hrs (unable to grasp) 0.5 hrs (loss of righting) 4 hrs (anesthesia)

Fig. 5

Phase II

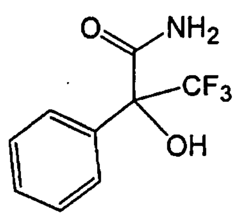
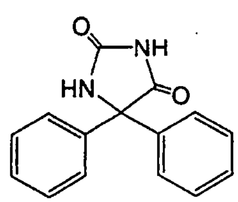
mouse data *Oral*	National Institute of Neurological Diseases and Stroke *Anti-Epileptic Drug Development Program*		
	MES ED_{50}	**ScMet ED_{50}**	**Rotorod TD_{50}**
 **ICM-I-40N(17)**	9.92 mg/kg (6.9-13.4)	38.57 mg/kg (24.6-51.9)	100 mg/kg
 **Phenytoin**	9.5 mg/kg (8.13-10.4)	>300 mg/kg	65.5 mg/kg (52.5-72.1)

Fig. 6

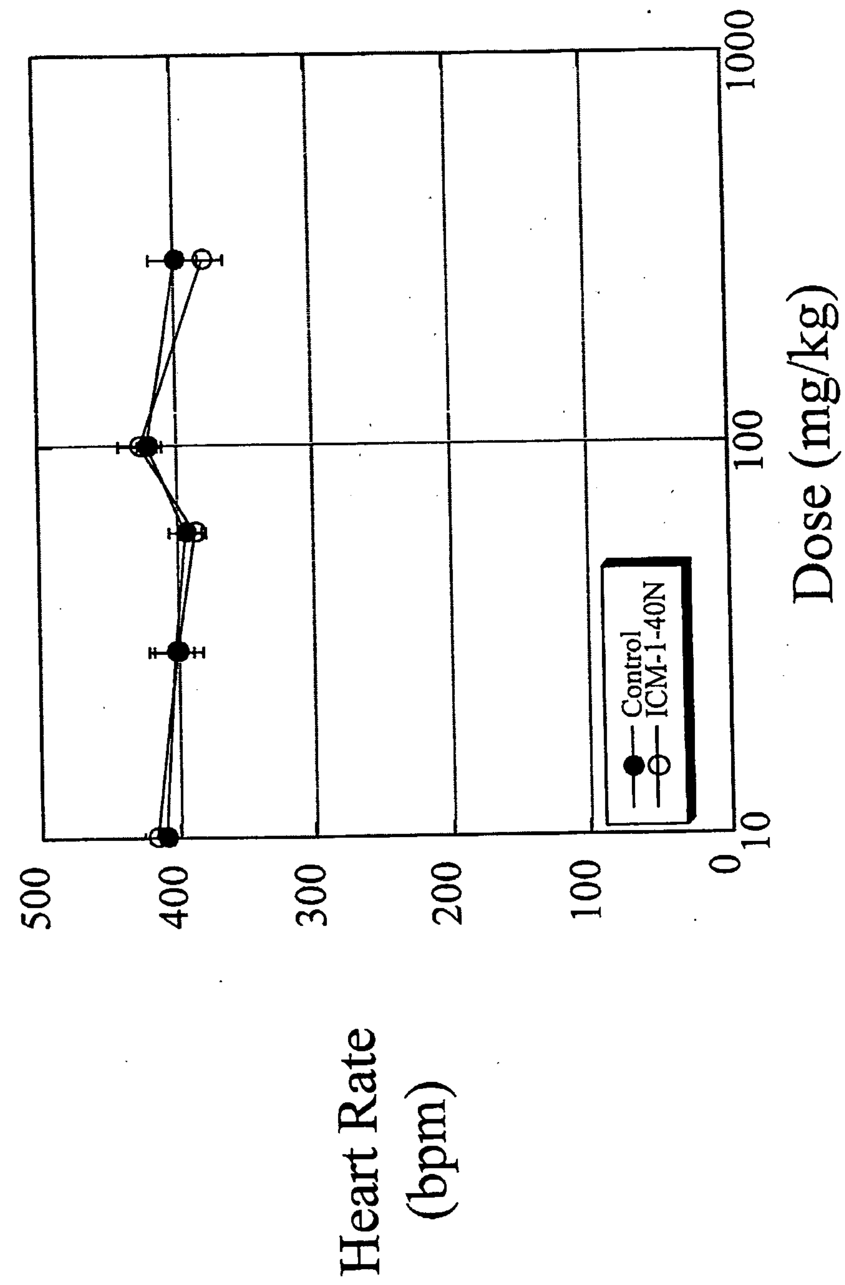

Heart Rate
(bpm)
500
400
300
200
100
0
10
100
1000
Dose (mg/kg)
Control
ICM-1-40N

Fig. 7

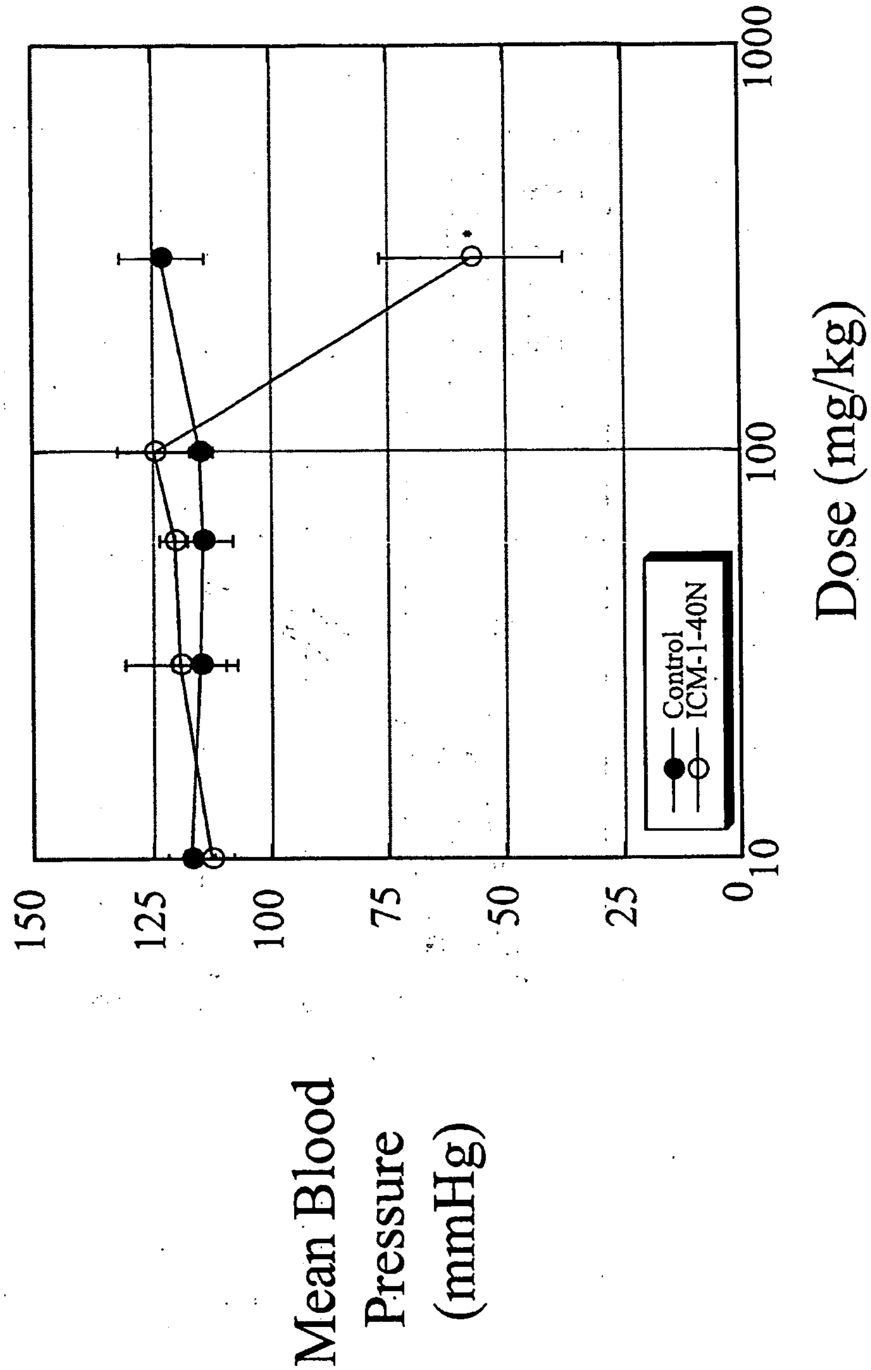
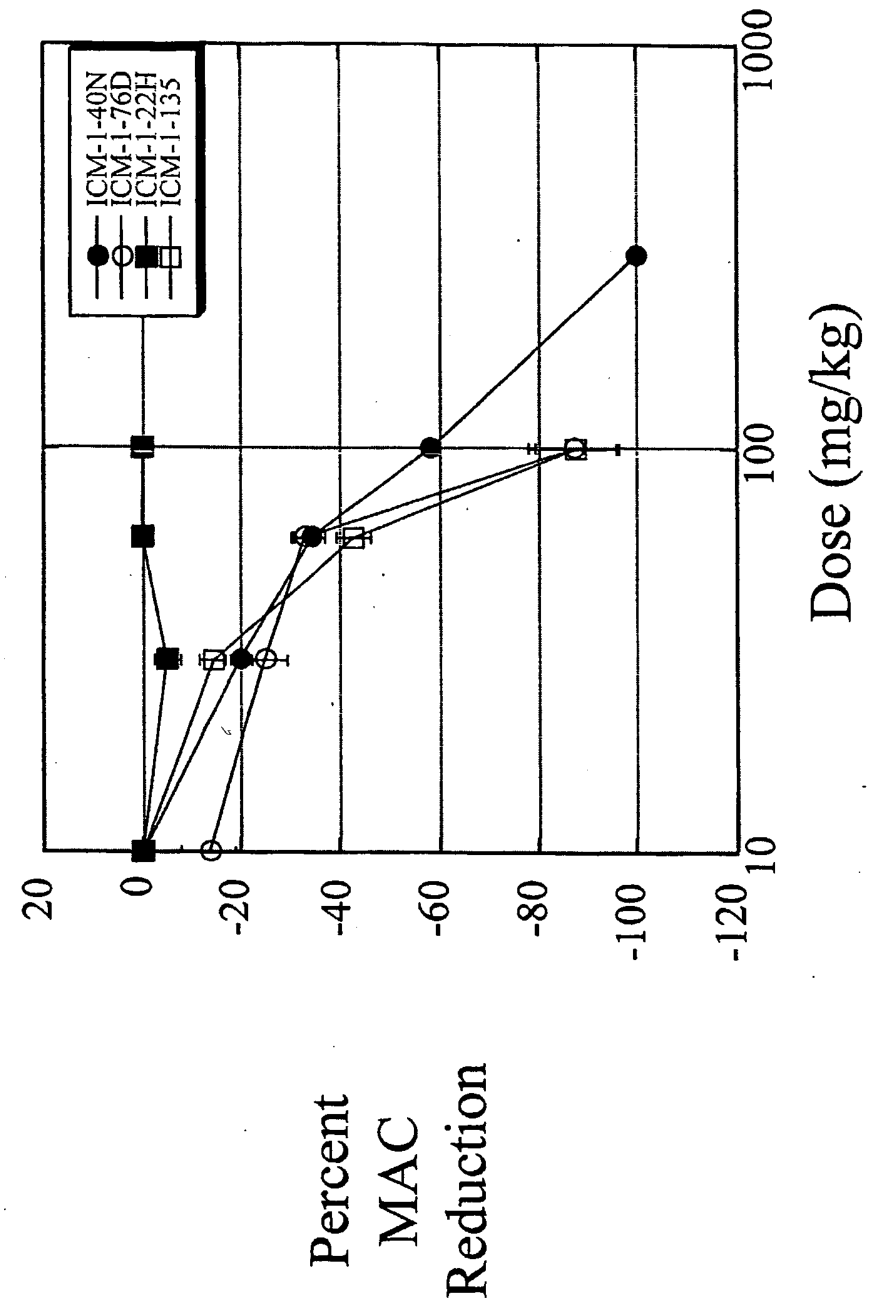

Mean Blood Pressure (mmHg)
150
125
100
75
50
25
0
10
100
1000
Dose (mg/kg)
Control
ICM-1-40N

Fig. 8


ICM-1-40N
ICM-1-76D
ICM-1-22H
ICM-1-135
Percent MAC Reduction
20
0
-20
-40
-60
-80
-100
-120
10
100
1000
Dose (mg/kg)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/11507

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CASONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,287,213 (BUSSCHOTS) 22 November 1966(22.11.66), column 1, lines 20-25.	1
X	BOWMAN et al. Trihalogenomethyl Compounds of Potential Therapeutic Interest, J. Chem. Soc. October 1964, pages 3841-3845, especially page 3841.	1
X	BURGERet al. 2- Trifluoromethyl alpha Amino Acid Esters, Building Blocks for Trifluoromethyl-Substituted Ureas, Thioureas and other Potential Biological Active Structures, Liebigs Ann. Chem., January 1994, Volumn 4, pages 399-406, especially page 400.	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 AUGUST 2002	18 SEP 2002

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Felicia D. Roberts SHAILENDRA KUMAR
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/11507

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CARR et al. 3-Halo 2-phenylglycinamide Hypnotics, 3-Halo-2-phenylglycinamide Hypnotics, November 1969, pages 989-994, especially page 990.	1-3, 5, 14
X	DALE et al. Alpha methoxy-alpha-trifluoromethylphenylacetic acid, a versatile reagent for the determination of Enantiomeric composition of alcohol and amines, September 1969, Volume 34, No. 9, pages 2543-2549, especially page 2548.	1-3, 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/11507

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K/31/045, 31/16, 31/65, 31/40, 31/55, 31/415;
CO7C/33/03, 233/05;
CO7D 209/34,36, 223/10, 233/02

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/212, 386, 418, 617, 627, 628, 730;
540/531; 548/484, 486, 320.5, 321.1; 564/170, 201, 203, 204; 568/809

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/212, 386, 418, 617, 627, 628, 730;
540/531; 548/484, 486, 320.5, 321.1; 564/170, 201, 203, 204; 568/809